UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/473,830	12/28/99	LEIDEN J	2844/53802

EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	15

028089
HALE AND DORR LLP
300 PARK AVENUE
NEW YORK NY 10022

HM12/0829

DATE MAILED: 08/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/473,830	Applicant(s) LEIDEN ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 6-13-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/473,830 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' preliminary amendment filed 6-13-01 has been entered. Claims 1-23 have been canceled. Claims 24-46 have been added. Claims 24-46 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transducing explanted and perfused hearts of C57BL/6 mice with 1.5x19E9 IU of AAV/CMV-lacZ for 15 minutes via catheter in the left common carotid artery, does not reasonably provide enablement for a method introducing a nucleic acid encoding any desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus for any period of time in any amount sufficient to stably and

efficiently transduce cardiomyocytes perfused by said artery or sinus in order to facilitate gene therapy approaches for a variety of cardiovascular diseases and conditions, wherein said AAV vector comprises at least one nucleic acid operably linked to a control region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 24-46 are directed to a method introducing a nucleic acid encoding any desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus for a period of time in an amount sufficient to stably and efficiently transduce cardiomyocytes perfused by said artery or sinus, wherein said AAV vector comprises at least one nucleic acid operably linked to a control region and said nucleic acid encodes said desired molecule. Claims 25-27 specify that the AAV vector transduces at least 10%, 40%, or 50% of the cardiomyocytes. Claims 28-39 specify that about 1x10E5 IU/g body weight to 1x10E9, 1x10E6 to 1x10E8, or 1x10E6 IU AAV/g body weight is infused for about 2-30 minutes, 5-20 minutes, or 15 minutes. Claims 41-46 specify the desired molecule encoded by the nucleic acid as recited in the claims.

The specification discloses transducing explanted and perfused hearts of C57BL/6 mice with 1.5x19E9 IU of AAV/CMV-lacZ for 15 minutes via catheter in the left common carotid artery, and the hearts were transplanted into the necks of syngeneic hosts and the arterial circulation reestablished by anastomosis of the transplanted aorta to the recipient carotid artery, The results suggest that 4 weeks after perfusion about 40% of cardiomyocytes were beta-

galactosidase positive, a number which increased to greater that 50% several weeks post transplantation.

The specification states "The ability to stably and efficiently program recombinant gene expression in cardiomyocytes facilitates gene therapy approaches for a variety of cardiovascular disease and conditions" and "The present invention is directed to a method of treating a cardiovascular condition by infusing an rAAV vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably efficient transduce the cardiomyocytes perfused to the artery or sinus" (see specification, page 1, 3). Although the new claims have been rewritten to "a method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus", the claims still read on *in vivo* **gene therapy** for a variety of cardiovascular diseases and conditions in light of the specification as discussed above.

The specification fails to provide adequate guidance and evidence for the correlation of a desired molecule encoded by the nucleic acid set forth above with a particular cardiovascular disease or condition. The specification fails to provide adequate guidance and evidence whether the desired molecule would be expressed and be present in a sufficient amount at the targeted site such that said desired molecule could provide therapeutic effect for a particular cardiovascular disease or condition in a patient *in vivo*.

The sufficient amount of desired molecules encoded by different genes for providing therapeutic effect in a patient *in vivo* for a particular cardiovascular disease or condition could

vary dramatically because of different functions of the desired molecules and the targeted cardiovascular disease or condition. The state of the prior art of gene therapy *in vivo* was not well developed and was highly unpredictable at the time of the invention. Verma et al., 1997 (Nature, Vol. 389, p. 239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics) indicates that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e.g. bridging pages 81-82). Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). The specification fails to teach how the desired molecule is correlated to a particular cardiovascular disease or condition and how to obtain sufficient expression of said desired

molecule at the targeted site so as to provide therapeutic effect for said particular disease or condition in a patient *in vivo*.

Further, it is not readily apparent how the expression of lacZ gene is correlative of enabling the expression of any therapeutic gene or desired molecule for treating a particular cardiovascular disease or condition. The specification fails to provide an enabling disclosure for the correlation of the expression of a lacZ, a reporter expressed by rAAV in mice for up to 8 weeks, and the expression of any therapeutic gene or desired molecule expressed by rAAV to provide therapeutic effect for a particular cardiovascular disease or condition *in vivo*. Thus, one skilled in the art at the time of the invention would not know how to use the claimed invention and would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.